Registration Decision RD2015-01

Metconazole

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Publications
Pest Management Regulatory Agency
Health Canada
2720 Riverside Drive
A.L. 6607 D
Ottawa, Ontario K1A 0K9

Internet: pmra.publications@hc-sc.gc.ca
healthcanada.gc.ca/pmra
Facsimile: 613-736-3758
Information Service:
1-800-267-6315 or 613-736-3799
pmra.infoserv@hc-sc.gc.ca

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Registration Decision for Metconazole

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is granting full registration for the sale and use of Metconazole Technical Fungicide and Tourney Fungicide, containing the technical grade active ingredient metconazole, to control several diseases on turfgrass on golf courses and sod farms.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

The detailed review for Metconazole Technical Fungicide can be found in Evaluation Report ERC2011-02, *Metconazole*. Metconazole Technical Fungicide and Tourney Fungicide were proposed for full registration in the consultation document[1] Proposed Registration Decision PRD2013-11, *Metconazole*. This Registration Decision[2] describes this stage of the PMRA's regulatory process for metconazole and summarizes the Agency's decision, the reasons for it and provides, in Appendix I, a summary of comments received during the consultation process as well as the PMRA's response to these comments. This decision is consistent with the proposed registration decision stated in PRD2013-11, *Metconazole*.

For more details on the information presented in this Registration Decision, please refer to the Proposed Registration Decision PRD2013-11, *Metconazole* and the Evaluation Report ERC2011-02, *Metconazole* that contains a detailed evaluation of the information submitted in support of this registration.

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[3] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its conditions of registration. The Act also requires that products have value[4] when used according to label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

1 "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

2 "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act.*

3 "Acceptable risks" as defined by subsection 2(2) of *Pest Control Products Act.*

4 "Value" as defined by subsection 2(1) of *Pest Control Products Act* "...the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (*a*) efficacy; (*b*) effect on host organisms in connection with which it is intended to be used; and (*c*) health, safety and environmental benefits and social and economic impact".

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children) as well as organisms in the environment (for example, those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management portion of Health Canada's website at healthcanada.gc.ca/pmra.

What Is Metconazole?

Metconazole is a triazole fungicide (demethylation-inhibiting fungicide) that inhibits sterol biosynthesis. The end-use product, Tourney Fungicide, contains 50.0% metconazole formulated as a water dispersible granule for use on turfgrass on golf courses and sod farms to control certain diseases.

Health Considerations

Can Approved Uses of Metconazole Affect Human Health?

Tourney Fungicide containing metconazole is unlikely to affect your health when used according to label directions.

Potential exposure to metconazole may occur through the diet (food and water) or when handling and applying the product. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed. The health effects noted in animals occur at doses more than 100-times higher (and often much higher) than levels to which humans are normally exposed when pesticide products are used according to label directions.

The technical grade active ingredient, metconazole, was moderately toxic to rats and highly toxic to mice when given as a single oral dose. It was of low acute dermal toxicity to rats and rabbits and of low inhalation toxicity to rats. It was moderately irritating to the eyes and non-irritating to the skin of rabbits. It was not a potential skin sensitizer to guinea pigs. The signal words, "DANGER – POISON" and "EYE IRRITANT" have been included on the label in light of these findings. Tourney Fungicide was found to be of slight oral acute toxicity and low dermal and inhalation acute toxicity in rats. It was minimally irritating to the eyes and non-irritating to skin of rabbits and not a dermal sensitizer in guinea pigs.

Health effects in animals given repeated daily doses of metconazole over longer periods of time were decreased body weights, effects in blood (regenerative anaemia) and microscopic changes to the liver, spleen and adrenal glands. There was no evidence that metconazole damaged genetic material. Skin tumours in male mice were observed following oral administration. There was no evidence of cancer in rats.

When metconazole was orally or dermally administered to pregnant rabbits, cranio-facial malformations were observed in fetuses. Limb-flexure malformations were observed in fetuses when metconazole was administered dermally to pregnant rabbits. These effects were observed at doses that were not toxic to the mother, indicating that the fetus is more sensitive to metconazole than the adult animal. Due to the serious nature of these endpoints, extra protective factors were applied during the risk assessment to further reduce the allowable level of human exposure to metconazole.

The risk assessment protects against the above effects by ensuring that the level of human exposure is well below the lowest dose at which the above effects occurred in animal tests.

Residues in Water and Food

Dietary risks from food and water are not of concern.

Aggregate dietary intake estimates (food plus water) revealed that the general population and all infants less than one year old, the subpopulation that would ingest the most metconazole relative to body weight, are expected to be exposed to less than 56% of the acceptable daily intake. Based on these estimates, the chronic dietary risk (non-cancer and cancer) from metconazole is not of concern for all population subgroups.

Acute dietary (food and water) estimate for females 13–49 years old was less than 83% of the acute reference dose, and is not of health concern. For all other subpopulations, an acute reference dose was not established; therefore an acute dietary intake estimate is not required.

The *Food and Drugs Act* prohibits the sale of adulterated food, that is, food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for *Food and Drugs Act* purposes through the evaluation of scientific data under the *Pest Control Products Act*. Food containing a pesticide residue that does not exceed the established MRL does not pose an unacceptable health risk.

No residue data are required to support the registration of metconazole for use in/on turfgrass on golf courses and sod farms in Canada. For the MRLs for this active ingredient on various crop commodities, please refer to the Maximum Residue Limit Database in the Pesticides and Pest Management section of Health Canada’s website.

Occupational Risks From Handling Tourney Fungicide

Occupational risks are not of concern when Tourney Fungicide is used according to the proposed label directions, which include protective measures.

Workers who mix, load or apply Tourney Fungicide, as well as workers re-entering freshly treated golf courses and sod farms, can come in direct contact with metconazole residues on the skin. Taking into consideration the approved personal protective equipment and engineered controls outlined in the Key Risk-Reduction Measures section below, the label statements, the number of applications and the expectation of the exposure period for handlers and workers, the non-cancer and cancer risks to these individuals are not of concern.

For bystanders, exposure is expected to be much less than that for workers and is considered negligible. Therefore, health risks to bystanders are not of concern.

Risks in Residential and Other Non-Occupational Environments

Non-occupational risks are not of concern when Tourney Fungicide is used according to label directions.

Adults and youth may be exposed to metconazole while golfing on treated courses. Based on the expected short-term duration of this activity, risk to golfers is not a concern. There were no cancer risks of concern.

Environmental Considerations

What Happens When Metconazole Is Introduced Into the Environment?

When used according to the label directions, metconazole does not pose an unacceptable risk to the environment.

Metconazole enters the environment when used as a fungicide on agricultural crops and on turfgrass. While metconazole generally breaks down relatively slowly, it can break down more rapidly in the presence of microorganisms in both aquatic and terrestrial environments. Metconazole dissolves readily in water and has the potential to move through soil and thus could reach groundwater under certain conditions. Specific instructions are provided on product labels to prevent carryover, groundwater contamination and runoff into aquatic habitats. Metconazole is unlikely to enter the atmosphere and be transported to areas far removed from where it was applied.

Metconazole is not expected to accumulate in the tissues of organisms.

Metconazole presents a negligible risk to terrestrial invertebrates including earthworms and honeybees, and freshwater invertebrates. As at high enough concentrations it could pose a risk to certain non-target organisms (terrestrial plants, birds, small wild mammals, amphibians,

freshwater fish, freshwater plants, marine invertebrates); spray buffer zones are specified on the label to protect terrestrial, freshwater and estuarine/marine habitats adjacent to treated areas. Toxicity statements are also specified on the product label for terrestrial plants, birds, mammals, and aquatic organisms.

Value Considerations

What Is the Value of Tourney Fungicide?

As a new fungicide active ingredient for use on turfgrass, Tourney Fungicide contributes to integrated pest management on golf courses and sod farms.

Measures to Minimize Risk

Registered pesticide product labels include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures being proposed on the label of Tourney Fungicide to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

Because there is a concern with users coming into direct contact with Tourney Fungicide on the skin or through inhalation of spray mists, anyone mixing, loading and applying must wear a long-sleeved shirt, long pants, shoes, socks and chemical-resistant gloves when handling up to 18.5 kg of Tourney Fungicide during groundboom application or when handling up to 2.1 kg of Tourney Fungicide during low pressure turf gun application. When handling more than 18.5 kg of Tourney Fungicide during groundboom application, mixer/loader/applicators must wear cotton coveralls over a long-sleeved shirt, long pants, shoes, socks and chemical-resistant gloves and must apply using a closed cab tractor. When handling more than 2.1 kg of Tourney Fungicide during low pressure turf gun application, workers must wear cotton coveralls over a long-sleeved shirt, long pants, shoes, socks and chemical-resistant gloves. The label also requires that workers do not enter treated golf courses and sod farms for 24 hours after application for transplanting, planting and slab harvesting activities. For other activities, the label requires that workers do not enter treated areas until sprays have dried.

Environment

For field sprayer application on turfgrass, spray buffer zones up to five metres in width are required to protect sensitive aquatic and terrestrial habitats from spray drift of Tourney Fungicide.

Other Information

The relevant test data on which the decision is based (as referenced in PRD2013-11, *Metconazole)* are available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa). For more information, please contact the PMRA's Pest Management Information Service by phone (1-800-267-6315) or by e-mail pmra.infoserv@hc-sc.gc.ca).

Any person may file a notice of objection[5] regarding this registration decision within 60 days from the date of publication of this Registration Decision. For more information regarding the basis for objecting (which must be based on scientific grounds), please refer to the Pesticides and Pest Management portion of the Health Canada's website (Request a Reconsideration of Decision) or contact the PMRA's Pest Management Information Service.

[5] As per subsection 35(1) of the *Pest Control Products Act.*

Appendix I Comments and Responses

1.0 Public comment:

Dermal Developmental Toxicity Study NOAEL Finding in the Rabbit

The results of a dermal developmental toxicity study in the rabbit with Metconazole Technical show maternal toxicity at the highest dose tested of 270 mg/kg/day. There was no embryo/fetal developmental toxicity noted at any dose tested. Therefore, the maternal NOAEL is 90 mg/kg/day and the embryo/fetal NOAEL is 270 mg/kg/day, the high dose tested. There were no test material related effects on development and, in particular, for craniofacial malformations.

PMRA has recently completed a study review and arrived at a different conclusion from that of the Study Director and registrant. According to PMRA, craniofacial and limb flexure malformations were observed at doses > 90 mg/kg/day. Consequently, PMRA found the LOAEL for developmental toxicity to be 90 mg/kg/day and the NOAEL to be 30 mg/kg/day. These conclusions were outlined in PRD2013-11, *Metconazole* (Page 16).

The registrant disagrees with this finding and conclusions, and agrees that the original interpretation provided by the Study Director is correct. While all rabbit malformations are rare, hydrocephaly is one of the most commonly observed malformations in rabbits. In both the mid- and high-dose groups, only one litter was affected. There are three studies in the historical control database with similar findings. The micropthalamia in two mid-dose fetuses from the same litter should be discounted because of a lack of dose response. Also, the eye formation is occurring much earlier in development than when hydrocephaly would occur. The flexure and hyperflexion should be considered a transient developmental variation as opposed to a malformation.

Based on the results of the rabbit dermal developmental toxicity study, the registrant believes the study NOAEL is 90 mg/kg/day (based on maternal toxicity) and that the appropriate endpoint for a dermal occupational risk assessment is 90 mg/kg/day.

PMRA Response:

After extensive consideration, the PMRA concluded that the craniofacial malformations in the dermal developmental toxicity study must be included in the risk assessment for the dermal occupational endpoints. The similarity of the malformations to those seen in the dietary developmental toxicity study and the history of craniofacial malformations after treatment with conazoles must be included in the weight of evidence for this risk assessment.

The registrant has stated that hydrocephaly is a commonly observed malformation in rabbits; however, in the historical controls it occurred at a mean of 0.1% of litters amongst 1394 litters, occurred at a maximum of 1.2% in any given study and was not present in the 25th or 75th quartile. In the dermal developmental toxicity study, it occurs in 4.5 and 4.3% of the litters (mid- and high-dose, respectively), in the presence of increased post-implantation loss at the high-dose, and hydrocephaly, domed heads and/or dilated brain ventricles are seen in all of the metconazole developmental toxicity studies, regardless of route of exposure. The occurrence of hydrocephaly at the mid- and high-doses of a dermal developmental toxicity in conjunction with other evidence of fetal toxicity is a cause for concern.

The registrant has stated that the incidences of micropthalamia should be discounted due to a lack of dose response. According to Harris and DeSesso[6] "… when embryolethal doses are reached, embryolethality increases at the expense of the other endpoints such as growth retardation and malformations. This can help to explain why an increase in malformations may exist in the low and/or mid dose groups, but not in the high dose group if the high dose group experienced a large increase in post-implantation loss." In the dermal developmental toxicity study, the high-dose group experienced a 194% increase in post-implantation loss compared to controls, and 19 late resorptions compared to one in the concurrent control group. Although there were higher numbers of fetuses in the high-dose group than the low- and mid-dose groups, this was due to a lower pregnancy rate at the lower doses. In light of the embyrolethality at the high-dose, dose-response was determined to be less important than the pattern of craniofacial malformations seen in various developmental toxicity studies and in many dose groups.

Finally, the registrant states that flexure and hyperflexion should be considered a transient developmental variation as opposed to a malformation. The flexure and hyperflexion effects are, in fact, classified as malformations by the study authors in the text of the study, in the historical controls for the developmental toxicity study, and in the 1989 WLI48271/KNF-S-474m study. According to Solecki et al.,[7] paw hyperextension "is more commonly observed in species with larger fetuses such as the rabbit. This was classified as a gray zone anomaly. Based on the availability of appropriate historical control data, the decision to classify as malformation (if the change is severe and considered as irreversible) or as variation (if it is slight) should be justified by each laboratory." While hyperextension is not identical to flexure and hyperflexion, the malformations are often grouped together. As such, in the absence of justification from the laboratory in question, the finding remains classified as a malformation.

6 Harris, SB and DeSesso, JM. Practical guidance for evaluating and interpreting developmental toxicity tests. Journal of Hazardous Materials. 39 (1994) 245-266.

7 Solecki, R et al. Harmonization of rat fetal external and visceral terminology and classification: Report of the Fourth Workshop on the Terminology in Developmental Toxicology, Berlin, 18–20 April 2002. Reproductive Toxicology 17 (2003) 625–637.

2.0 Public Comment:

Carcinogenicity Study and Q_1* Finding in the Mouse

Clinical observation and historical control data were collected and submitted as part of a Weight-of-Evidence document to support the position that skin tumors observed in the male mice were a result of chronic irritation.

The Weight-of-Evidence presented supports the position that the skin/subcutis (subcutaneous) tumors observed were not induced by the compound, but rather occurred as a result of induction of reactive skin wounds / inflammation from in-cage fighting.

The skin tumor incidence at the high-dose does slightly exceed the concurrent and historical control data (mostly using individually-house mice), but the remaining evidence does not support a carcinogenic mode of action (MOA) for metconazole.

PMRA has recently completed a review of the Weight-of-Evidence document and has maintained their conclusion that the proposed MOA is not supported by the data provided. PRD2013-11, *Metconazole* suggests that there is insufficient evidence to discount a treatment-related cause, even though there is no statistically significant increase in tumor formation and the low- and mid-dose groups fall within historical control values for this tumor type.

The registrant disagrees with this conclusion and wishes to reiterate the arguments set forth in the Weight-of-Evidence document illustrating the lack of support for a metconazole-induced MOA for the skin tumors.

PMRA Response:

As stated in the Weight-of-Evidence document referred to above, in response to the registrants' claim that the skin/subcutis (subcutaneous) tumors occurred as a result of induction of reactive skin wounds/inflammation from in-cage fighting, the PMRA had requested clinical observation data from the oncogenicity study in order to assess whether there was a possible correlation between incidences of in-cage fighting and tumour incidence.

After correlating cage assignment against clinical observations and tumour incidences (following the company's assertion that less dominant mice within a cage were more likely to exhibit sores leading to a greater opportunity to develop sarcomas) it was noted that, while all tumour-bearing animals exhibited sores, there was a large variation in the numbers of sores and the length of time an animal exhibited a sore before exhibiting a mass in the area a tumour was found. For example, while animal 238 in the high-dose group exhibited sores on the left shoulder for eight weeks and sores on the back for ten weeks before being sacrificed for a skin subcutis tumour on its left shoulder at 89 weeks, animal 239 exhibited a sore on the dorsal hind left leg on weeks 86-87 only and a sore on its back on week 88 only, before exhibiting a large moveable mass on its left dorsal hind surface at week 88, with sacrifice at week 89 due to a skin subcutis tumour.

The registrant submitted lab-specific historical controls for skin sarcomas in group-housed mice in the interest of controlling for in-cage fighting. The mean incidence of skin sarcomas was 1.7%, the mean incidence of fibromas/fibrosarcomas was 1.25% and the mean incidence of sarcomas combined with fibromas and fibrosarcomas was 2.98%. The minimum – maximum range in each of the cases was 0.00–6.86%. The registrant asserted that the incidence of benign fibroma in the control group could be grouped with fibrosarcomas and sarcomas in the treated groups for statistical purposes.[8]

Accepting the assertion that the control incidence of fibroma can be considered part of the sarcoma incidence, the control incidence is within the range of what would be expected (based on the historical control mean) whereas all the treated groups fall above the mean historical control. Comparing against the minimum – maximum range, the low- and mid-dose groups fall within historical controls while the high-dose group falls outside historical controls.

The registrant has stated that while the high-dose tumours are outside historical controls, the tumours are a random occurrence. It is the PMRA's position that while rare and not statistically significant, a tumour incidence that is above historical controls and demonstrates a dose-related increase in incidence should be considered biologically significant. However, as the tumour incidences at the lower doses are below historical controls and there is no evidence of skin tumours with other conazoles, a threshold-based approach to the assessment of skin tumours in male mice is considered acceptable. The dietary reference dose (i.e., the acceptable daily intake (ADI)) and the selected margins of exposure (MOEs) for occupational and bystander exposure provide a sufficient margin to this endpoint. As such, a linear low-dose approach is not necessary to characterize cancer risk.

3.0 Public Comment:

Acceptable Daily Intake (ADI) Endpoint Determination

Based on scientific rationales provided to PMRA under a previous application, the registrant disagrees with the basis for establishment of the General Population Acceptable Daily Intake (ADI) toxicology endpoint. The rat oncogenicity study was utilized to set an ADI of 10 ppm (0.44 mg/kg/day) [*sic*], however the data indicate the NOAEL of the rat oncogenicity study to be 100 ppm (4.61 mg/kg/day).

[8] In the individual animal pathology reports from the original study (PMRA #1405626), the low-dose sarcomas are classified as "possibly fibrosarcoma" and "fibrosarcoma". The tumours in the higher doses are described with more detail. For example, "a pleomorphic proliferation of round/oval/spindle cells infiltrating subcutis and muscle".

PMRA Response:

The ADI for the general population (excluding females aged 13-49) is 0.0044 mg/kg bw/day, based on the standard uncertainty factor of 100 to account for the inter-species extrapolation and intra-species variability. The *Pest Control Products Act* factor is reduced from 10-fold to 1-fold because the database is considered adequate with regards to characterize pre- and post-natal toxicity, and the end-point of concern with respect to pre- and post-natal toxicity has been addressed in a population specific risk assessment (i.e. females aged 13 – 49). The composite assessment factor is 100.

The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{0.44 \text{ mg/kg bw/day}}{100} = 0.0044 \text{ mg/kg bw/day}$$

In determining the ADI for the general population (excluding females aged 13-49), the results of the rat chronic and rat oncogenicity studies were considered together. The NOAEL of 0.44 mg/kg bw/day was established for the rat oncogencity study, based on incidences of adrenal cortex vacuolation and clear cell foci and necrotic inflammatory foci in the liver at the LOAEL of 4.29 mg/kg bw/day.

In the review of the chronic rat toxicity study, the LOAEL for the rat chronic toxicity study was set at 100 ppm (4.29 mg/kg bw/day) in males, based on an increase in cortical vacuolation of the adrenal glands and necrotic inflammatory foci in the liver, and 300 ppm in females based on decreased platelet counts, increased spleen weights, increased liver histopathology, increased cortical vacuolation foci in the adrenals and increased adenomas of the mammary tissue. Thus, the driving factor in the setting of the LOAEL in both the chronic and oncogenicity studies was changes to the liver and adrenal glands. These were the target organs in every study, independent of species.

The combined incidences of cortical vacuolation in the adrenals from both the chronic and oncogenicity studies show a clear increase in histopathological change in the adrenal cortex in males and females at 100 ppm, as was the occurrence of necrosis and clear cell foci in males at 100 ppm. This was further supported by adverse, treatment-related changes in reproductive parameters and oligiospermia in other studies at 100 ppm.

In summary, the combined LOAEL for the rat chronic and oncogenicity studies was determined to be 100 ppm in males and females, based on vacuolation of the adrenal cortex in males and females, and necrotic inflammatory foci and clear cell foci in the livers of males. The NOAEL was 10 ppm (0.44 mg/kg bw/day).

4.0 Public Comment:

Occupational/Short-Term Risk Assessment Endpoint Determination

Based on scientific rationales provided to the PMRA under a previous application, the registrant believes that the rat developmental toxicity study with a NOAEL of 16 mg/kg/day should be utilized for assessment of occupational inhalation exposures and/or the short term dietary assessment of sensitive subpopulations. PMRA has chosen instead to utilize an endpoint of 2 mg/kg/day taken from a rabbit developmental toxicity study that has been shown to be scientifically unreliable.

PMRA Response:

The NOAEL of 2 mg/kg bw/day from the rabbit oral developmental toxicity study is considered the most appropriate endpoint for short- and intermediate-term inhalation risk assessment. The NOAEL is based on the observation of craniofacial malformations in fetuses at the next higher dose level. The worker population could include females of child bearing age (13–49) and therefore these endpoints were considered appropriate for the occupational risk assessment. For this reason, the target MOE is 1000, accounting for standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability, as well as the additional 10-fold factor to protect the unborn children of exposed female workers for the reasons outlined in the *Pest Control Products Act* section of PRD2013-11, *Metconazole*.

The registrant submitted a "Review and Evaluation of the Data on Metconazole Developmental Toxicity in Rabbits". A summary of the author's comments appears in quotations below and is followed, in turn, by the PMRA response:

1. "Craniofacial malformations noted in the rabbit developmental toxicity studies were seen in all studies, but were not the majority of malformations. Therefore, craniofacial malformations do not appear to be the most sensitive type of morphological effect resulting from metconazole treatment in studies from either laboratory."

Craniofacial malformations have been noted in a number of other conazoles. As such, the weight of evidence, when presented with a number of studies indicating malformations in the same source tissue that increase in severity with increasing dose, is sufficient to consider craniofacial malformations a serious concern.

2. "Limitations in the studies, including lack of clear dose-response, lack of clear pattern of related foetal abnormalities, variable rates of malformations in control animals, presence of severe malformations in offspring from some control animals as well as in offspring from treated animals, preclude the use of the developmental data from being used to establish LOAELs and NOAELs based on developmental effects."

The PMRA did not find there to be deficiencies that would affect the outcome of the studies. The studies were well-executed and performed according to the guidelines of the time. Furthermore, the historical controls for the studies were well characterized and malformations in concurrent control animals fell within the historical controls, while malformations determined to be treatment-related fell outside the historical controls from that time period.

5.0 Public Comment:

Recommendation on the *Pest Control Products Act* Factor

As outlined in PRD2013-11, *Metconazole*, the *Pest Control Products Act* factor was retained at 10-fold based on the perceived observation of "severe" effects, including craniofacial malformations.

The registrant has provided studies and scientific rationales disputing the finding of severe metconazole-induced craniofacial alterations. The most recent evidence for the elimination of the *Pest Control Products Act* factor comes from the recently reviewed dermal developmental study in the rabbit. As outlined above, the registrant believes this study confirms the lack of such malformations; therefore, there is no justification for the retention of the *Pest Control Products Act* factor at 10-fold.

PMRA Response:

As explained in PRD2013-11, *Metconazole* and further noted in responses to comments 1 and 4 above, the PMRA maintains that the craniofacial malformations observed in the developmental toxicity studies by both the oral and dermal routes cannot be discounted. As such, the inclusion of these findings in the risk assessment is warranted as is the 10-fold *Pest Control Products Act* factor.